REMARKS

Claims 1-5 and 7-36 are pending and were rejected. Claims 1-5, 7-8, and 14-19 are currently amended. No new matter has been introduced with this amendment. Support for these amendments can be found in the previous claims and page 12-13 and 23 of the specification.

For the sake of clarity, the rejections of the presently outstanding Office Action are addressed below in the order in which they were presented.

Response to Claim Rejections – 35 USC § 103

Claims 1, 35 and 36 were rejected under 35 USC § 103 as being unpatentable over Kovacs et al. (5,981,268) in view of Luo et al. (Bio-Medical Materials and Engineering), or Franks (4,968,623). The Examiner was not persuaded by Applicants' arguments and maintains the rejection that "it would have been "obvious to one of ordinary skill in the art at the time the invention was made to provide the detector array of the primary reference with a thin film of diamond-like carbon material to improve cell adhesion to the surface of the detector array."

Applicants reiterate and extend the previous arguments because the arguments provided by the Office show a misunderstanding of the invention. Applicants have also provided a declaration by the lead inventors, as further evidence to the Office of the non-obviousness of the invention.

The Office agreed that "Claim 1 differs [from Kovacs et al] by reciting that the chip platform also includes a thin patterned film applied to the protective film." Office Action, page 3. The Office then employs the two references of Luo et al. and Franks et al. as disclosing "that it is known in the cell culture art to employ a thin film of diamond-like carbon material to improve cell adhesion to a culture surface." Ibid. Then in conclusion, the Office states "[w]ith respect to claim 36, the use of culture adhesion proteins is notoriously well known in the art to facilitate and/or selectively culture cells on a culture surface. As a result, it would have been obvious to one of ordinary skill in the art to provide the device of the modified primary

reference with culture adhesion proteins for the known and expected result of manipulating and/or facilitating the adhesion of the cultured cells to the detector surface." Office Action, page 4.

Applicants respectfully point out again that the two cited references, Luo et al. or Franks et al., do not disclose patterning the thin-film of diamond-like carbon (DLC) material. The Office agreed that the patterned films were not disclosed in any reference, and then simply concludes it would have been obvious to use a thin film. It appears that the Examiner has not given patentable weight to the fact, unlike the prior art, according to Claim 1 the thin diamond-like carbon film is patterned so as to pattern cellular growth. Applicants had provided specific arguments and provided reference to page 12 of the specification which discusses the thin patterned film as a specific aspect of the claimed invention. Furthermore, Applicants had previously amended claim 1 to reflect that sustained cellular growth only occurs on the patterned film.

Thus Applicants are confused why later the Examiner on page 8 of the Office Action states that "it is noted that the features upon which applicant relies (i.e., the cell patterning disclosed in the instant specification) are not recited in the rejected claim(s)." Applicants submit that the feature limitations recited in Claim 1 of "**a thin patterned film** comprising diamond-like carbon is applied to the protective film **to pattern cellular growth, wherein sustained cellular growth only occurs over the thin patterned film**," overcome this aspect of the rejection.

The Office concluded that "it would have been obvious to one of ordinary skill in the art to provide the device of the modified primary reference with culture adhesion proteins for the known and expected result of manipulating and/or facilitating the adhesion of the cultured cells to the detector surface." Again, it appears that the Examiner is not giving patentable weight to the claim limitation of a patterned film for patterning cellular growth. Applicants were the first to demonstrate that a thin patterned film of diamond-like carbon could be used to pattern cellular growth. Patterning cell growth is more than "manipulating and/or facilitating the

adhesion of the cultured cells to the detector surface" to allow them to grow. Moreover, one of ordinary skill in the art knows that cellular growth is difficult to control, let alone to pattern and sustain such patterned growth for any extended period of time. Furthermore, the ability of diamond-like carbon to maintain cellular growth in only the patterned area, while the unpatterned area remains clear of cellular growth had not been shown before and was not known. This unexpected result is what allowed the inventors to move forward the invention. The attached declaration provides further evidence of this unexpected result.

Again, while both references teach the use of DLC as a biologically compatible material suitable for use in cell culture, neither Luo et al. or Franks et al., nor any other cited reference, teach that application of DLC could be used to direct or pattern cell growth as Applicants have claimed. This feature is discussed specifically on page 12 of Applicants' specification and shown below.

> "The patterning of film 30 is designed to control the connections between neuronal cells in predetermined ways. The material used in patterned film 30 is designed to facilitate neuronal attachment and growth, so that the areas of the device lacking patterned film 30 have essentially no neuronal growth. Accordingly, a neuronal body may be selected for engagement by a dendrite at a pre-determined distance from the center of the neuron by virtue of the arrangement of patterned film 30. The patterned film 30 may also be formed of an electrically conductive metal to be useful for delivering an electrical signal to a pre-selected neuron."

Applicants also point to Figure 6, which shows patterned growth of neurons on DLC while there is little to no growth on areas with no DLC.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Applicants respectfully submit that none of the cited references. teach or suggest a cell culture apparatus having a thin patterned film that patterns cell growth, as claimed by Applicants. As such, the Examiner has failed to establish a *prima facie* case of obviousness with regard to claim 1, because the combination of Kovacs et al. in view of Franks et al. or Luo et al. does not teach each and every feature of Applicants' claimed invention. None of the references teaches or suggests the patterned film of diamond-like carbon for sustained patterned

growth of cells. See Applicants' arguments in previous responses. Moreover, the combination of all three references does not result in Applicants' claimed invention of a cell culture apparatus having a thin patterned film that directs sustained patterned cell growth. Therefore, the Office has not shown a *prima facie* case of obviousness because the combined references do not produce the claimed invention.

Applicants' previous response presented arguments that it was not shown by Kovacs et al. and not obvious to pattern and grow cells directly on the CCD array. Based on the Office Action's arguments, it is apparent that the Office has not fully grasped that the CCD array is used in the claimed invention for electrostatic detection, not photodetection as it is used in Kovacs et al. Applicants point the Examiner to column 12, second paragraph, lines 27-30 of Kovacs et al. which describes that "[i]n the particular embodiment shown in FIG.5, the monolithic structure includes and integrated photosensor 57, for example, a photodiode or CCD." The mention of CCDs is used for photodetection. See also claim 10 of Kovacs et al. which claims an "optical sensor." Thus, Kovacs et al. employs an integrated CCD in some embodiments for purely *optical* imaging of the cell.

Indeed, in all of column 7, and later in column 11, paragraph 2, describe detection of signals in the cells is performed by the microelectrodes. See especially column 7, lines 47-65, which at the outset states, "It is a feature of the invention that each of the microelectrodes is sufficiently small to enable monitoring of an individual cell and its cellular membrane."

In contrast, Applicants' invention uses the CCD array for electrostatic detection of the cells grown on its surface. See pages 20-23 of the specification, especially paragraph [077], which describes that the cells are used as an integral part of the entire biosensor. To this end and to clarify for the Office, Applicants have currently amended the Title of the present application and the preamble of the claims to reflect that the claimed invention is a biosensor, the amendment which finds support as cited above.

Therefore, because the Office has not shown a *prima facie* case of obviousness the claims cannot be said to be obvious in view of the cited references. In light of the foregoing

arguments, Applicants respectfully request that the rejection of claim 1, 35 and 36 under 35 U.S.C. § 103 be withdrawn and the claims allowed.

Response to Claim Rejections – 35 USC § 103

Claims 2-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kovacs et al (US 5,981,268) in view of any of Luo et al (Bio-Medical Materials and Engineering) or Franks (US 4,968,623) taken further in view of Miyamoto (US 5,702,915).

Applicants disagree that the combination of the cited references of Kovacs et al, and Luo et al, or Franks et al., and further in view of Miyamoto et al., teach, suggest or motivate the combination of various elements to make Applicants' claimed invention or that it would have been obvious to combine these references to make Applicants' claimed invention. Applicants reiterate that none of the cited references teach or suggest a cell culture apparatus having a thin patterned film that patterns cell growth on a CCD array, as claimed by Applicants. To state it more plainly, the Office has not shown a *prima facie* case of obviousness because the combined references, Kovacs et al., Franks et al. or Luo et al., do not produce the claimed invention. The addition of a fourth reference, Miyamoto et al. does not cure this defect.

Applicants disagree with the Examiner's reading of Miyamoto as disclosing "that it is known in the cell culture art to interface a cell culture with a CCD array (1)…" Office Action at 4. Indeed, Miyamoto states that "[a]fter charge coupled device (CCD) have been made available, the element for taking photographs of images of a solid has developed and has been enormously improved…Because of these advantage[s], the element for taking photographs of images of a solid is taking over camera tubes in the field of broadcasting and so on." Miyamoto clearly is referring to using a CCD to take photographs of a solid and cell activity (col. 1, line 54) and not referring to any known technique of "interfac[ing]" cells with a CCD array for electrostatic detection.

Neither does Miyamoto teach or suggest interfacing cells with a CCD array as claimed by Applicants. Miyamoto teaches the use of a cell culture container positioned on the upper surface of a solid-state area image pickup element, but does not teach or suggest the use of a

thin protective film over the CCD and/or a thin patterned film to pattern cellular growth. Heretofore, it has not been shown that thin films could be used and that cells would remain viable for long-term growth (upwards of days and weeks at a time). Thus, the Office has not presented a *prima facie* case that it would have been obvious to one of skill in the art that the combination of the four references would produce Applicants' claimed invention.

Therefore, the claims are not obvious in view of the prior art references and the rejection should be withdrawn. In light of the foregoing arguments, Applicants respectfully request that the rejection of claims 2-33 under 35 U.S.C. § 103 be withdrawn and the claims allowed.

CONCLUSION

Accordingly, Applicants respectfully request the entry of the claims as amended and provided herein. A petition for extension of time for the third month of extension and the fee for $555 is attached. The Commissioner is hereby authorized to deduct a total of $555.00 from Deposit Account 120690. Applicants believe all fees necessary for this amendment are submitted herewith. If any additional fee is necessary for entry of this amendment, the Office is hereby authorized to deduct that charge from Deposit Account 120690.

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned at (510)495-2456.

Respectfully submitted,

Dated: September 3, 2009

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